Peri-implantitis: A Comprehensive Overview of Systematic Reviews

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The objective of this systematic review was to perform a comprehensive overview of systematic reviews and meta-analyses pertaining to peri-implantitis in humans, including the prevalence and incidence, the diagnostic findings, microbial findings, effects of systemic diseases, and treatment of peri-implantitis. Electronic databases were searched for systematic reviews and meta-analyses of peri-implantitis. In view of the limitations of the included systematic reviews, the outcome of this overview suggested that (1) occurrence of peri-implantitis was higher in patients with periodontitis, in patients who smoke, and after 5 years of implant function; (2) the microbial profile of peri-implantitis was different from periodontitis; (3) risk for peri-implantitis was higher in patients with uncontrolled diabetes and cardiovascular disease; (4) there was no strong evidence to suggest the most effective treatment intervention for peri-implantitis, although most peri-implantitis treatments can produce successful outcomes; and (5) postimplant maintenance may be crucial in patients with a high risk of peri-implantitis.

Key Words: dental implant, peri-implant, bone loss, peri-implantitis, systematic review

INTRODUCTION

Dental implants have become widely used in restoring the fully or partially edentulous patient. They have become a predictable alternative to fixed and removable partial dentures and were often the treatment of choice.[1,2] High implant survival rates of 92.8%–97.1% over a follow-up period of 10 years indicated that dental implants were a valid treatment option for the dental rehabilitation of the partially and fully edentulous patient.[3,4] However, despite its high survival rates, dental implants were prone to biological complications like peri-implantitis.[5] Peri-implantitis was described as a destructive inflammatory lesion affecting hard and soft tissues of the osseointegrated implant causing bone loss and peri-implant pocketing.[6] Peri-implantitis can be asymptomatic, showing only signs of bleeding on probing, attachment loss, and bone loss. Or peri-implantitis can manifest clinical signs of increasing probing depths, suppuration, draining sinus, and peri-implant mucosal swelling or recession.[7] If peri-implantitis was not detected early and treated, the bony destruction could extend the whole lengthen of the implant, resulting in loss of implant stability.[7] Thus, early peri-implantitis detection and effective treatment is crucial in a practice that focuses on implant rehabilitation of the edentulous patient.

Some studies indicated that patients, who have lost 1 implant due to peri-implantitis, were more prone to implant failure.[8,9] Patients with periodontal disease seemed to experience more implant loss due to peri-implantitis than periodontally healthy patients.[10,11] Patients who smoke were also at risk for peri-implantitis, but non-smoking patients can develop peri-implantitis, and not all smoking patients develop peri-implantitis.[12,13] Radiographically, patients with periodontitis and smokers have also reported significantly more marginal bone loss around their implants.[14] Thus, these factors predisposing peri-implantitis should be closely examined when treatment planning the dental patient for implants.

The aim of this comprehensive review was to provide a systematically derived overview of systematic reviews pertaining to different aspects of peri-implantitis that will help the clinician understand and manage peri-implantitis in their practice.

MATERIAL AND METHODS

Focused questions

- What is the prevalence, incidence, or risk of peri-implantitis in periodontal health and disease?
- What factors are associated with peri-implantitis?
- What treatment intervention is most effective in treating peri-implantitis?

Literature and study design

A systematic search was conducted of PubMed, Embase, Web of Science, Cochrane library, and Google Scholar for systematic reviews and meta-analyses of peri-implantitis published from October 1989 until October 2016. The keywords used for the

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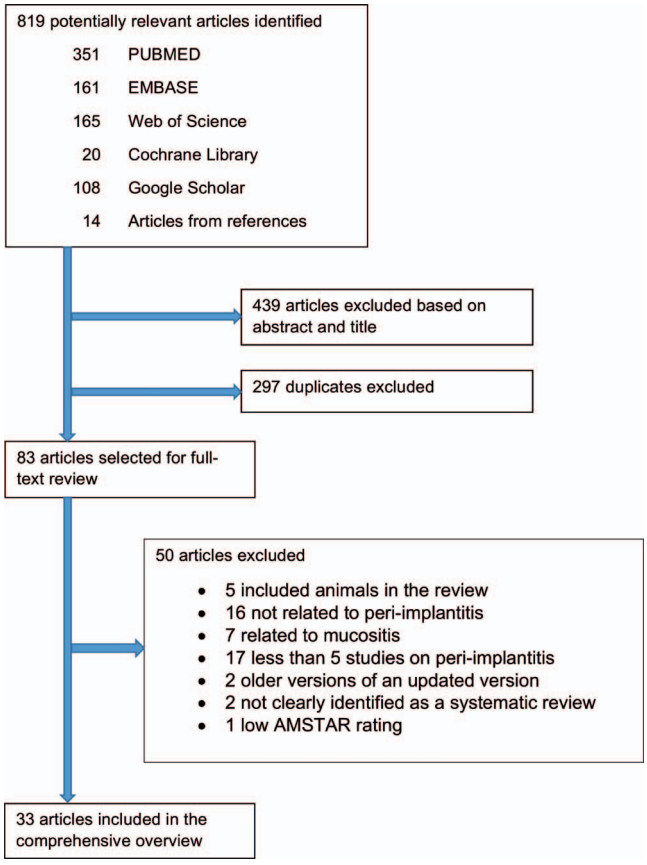

Figure 1. Search strategy for peri-implantitis.

search were '"peri-implantitis" OR "peri-implant disease"' AND '"systematic review" OR "meta-analysis."' Gray literature was also searched on Google Scholar using advance search to find articles with the word "peri-implantitis" and then again for "peri-implant". Both searches were done with at least 1 of the words used: "systematic review" or "meta-analysis". In addition, hand-searching was conducted on the reference list of selected meta-analyses and systematic reviews.

Inclusion criteria

- The review must be identified as a meta-analysis or a systemic review in the abstract or title.
- All definitions of peri-implantitis included were specified as one of the following: (1) the consensus definition agreed upon in the 1st European Workshop on Periodontology,[15] (2) the presence of inflammation in the peri-implant mucosa, as indicated by bleeding and/or pus on probing, with loss of supporting bone,[6] (3) a continuous marginal bone loss beyond biological bone remodeling or more than 2 mm; and with signs of inflammation like purulence, bleeding on probing, and more than 6 mm probing pocket depth, (4) an incidence of probing pocket depth $\geq$5 mm with bleeding on probing and or suppuration and radiographic signs of bone loss of $\geq$2.5 mm or bone loss extending $\geq$ the first 3 threads,[16] (5) peri-implant probing depth $>$5 mm with bleeding on probing, or (6) peri-implant crestal bone loss at osseointegrated dental implants in conjunction with inflammation of peri-implant mucosa.[17]
- The focused questions or review objectives must pertain to peri-implantitis in humans.
- If peri-implant mucositis was included in the review, only the peri-implantitis data was included.
- Only systematic reviews or meta-analyses that reviewed 5 or more studies pertaining to peri-implantitis were included.
- Based on the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) checklist,[18] only studies scoring $>$3 were included.

Exclusion criteria

- Reviews including animal studies were excluded.
- Marginal bone loss in the absence of inflammation or marginal bone loss with no mention of peri-implantitis or gingival condition were excluded.
- Peri-implant mucositis were excluded.
- Comments, editorials, posters, and critical reviews of systematic reviews were excluded.

Screening, selection, and data extraction

Two reviewers (MT and JC) independently screened the title and abstract to exclude articles that clearly were not systematic reviews or meta-analyses pertaining to peri-implantitis. The inclusion and exclusion criteria previously described were independently applied by the reviewers (MT and JC) while analyzing the full-text for inclusion. Disagreements were resolved by discussion with a third reviewer (JBS).

One reviewer (MT) extracted the data using a previously pilot tested data extraction form, and 2 other reviewers (BEB and JC) independently checked the extraction data for precision and entirety. Disagreements were resolved through discussion.

Assessment of quality of systematic reviews and meta-analyses

The methodological quality of a systematic review can be evaluated using the AMSTAR tool.[18] AMSTAR has been specifically developed to overcome the shortcomings of previous measurement tools that were lengthy and complicated to use.[18] AMSTAR consists of 11 questions; each question is given a score of 1 if the criteria is satisfied, or a score of 0 if the criteria is not met, unclear, or not applicable.[19] The sum of the scores from each question results in an overall score reflecting the review quality.[19] Although controversial, AMSTAR characterized systematic review quality at 3 levels: 8 to 11 for high quality, 4 to 7 for medium quality, and 0 to 3 for low quality.[19] The AMSTAR tool was used to assess the quality of the selected systematic reviews. The scoring used the AMSTAR checklist[18] and was performed by 2 reviewers (MT and BEB). Disagreements were resolved by discussion with a third reviewer (JC). Reviews scoring 3 or less were excluded in this overview.

Results

The search yielded 351 reviews in PubMed, 161 in Embase, 165 in Web of Science, 20 in Cochrane Library, and 108 in Google Scholar. After the initial abstract and title screening, 59 reviews were selected from PubMed, 39 from Embase, 54 from Web of

TABLE 1

Characteristics of included articles for peri-implantitis*

Study	Focused Question/Aims	Data Reported	AMSTAR Rating
Atieh et al[20]	What is the prevalence of peri-implant diseases in general and high-risk participants over 5 years?	Prevalence of peri-implantitis	High
Chan et al[21]	What are the radiographic and clinical outcomes of different surgical interventions for the treatment of peri-implantitis?	Treatment of peri-implantitis	High
Daugela et al[22]	1. What are the overall treatment outcomes of reconstructive procedures in treating peri-implantitis? 2. Does the use of barrier membranes or submergence of the healing site provide beneficial clinical outcomes in the treatment of peri-implantitis?	Treatment of peri-implantitis	High
de Waal et al[23]	Do fully edentulous subjects with dental implant-supported reconstructions show a similar prevalence of peri-implant disease (ie, peri-implant bleeding, peri-implant mucositis, or peri-implantitis) compared to partially edentulous subjects with dental implant-supported reconstructions?	Prevalence of peri-implantitis	High
Derks and Tomasi[24]	In patients with osseointegrated dental implants, what are the prevalence, extent, and severity of peri-implant diseases?	Prevalence of peri-implantitis	High
Duarte et al[25]	Could cytokine levels in the peri-implant crevicular fluid be used to distinguish between healthy implants and implants with peri-implantitis?	Diagnostic findings for peri-implantitis	Medium
Esposito et al[26]	To identify the most effective interventions for treating peri-implantitis around osseointegrated dental implants	Treatment of peri-implantitis	High
Faggion et al[27]	To demonstrate the application of network meta-analysis in implant dentistry using peri-implantitis treatment	Treatment of peri-implantitis	High
Faggion et al[28]	To assess the clinical effect of different non-surgical treatments for peri-implantitis using a network meta-analytic approach	Treatment of peri-implantitis	High
Faot et al[29]	Do patients with peri-implantitis present higher prevalence of any specific inflammatory cytokine in peri-implant crevicular fluid compared with healthy individuals? Can peri-implant crevicular fluid be used as a predictor for incipient peri-implantitis?	Diagnostic findings for peri-implantitis	Medium
Graziani et al[30]	What is the quality of scientific studies evaluating preventive approaches to peri-implant diseases, in terms of reporting, outcome measurements, and methods? What is the quality of scientific studies evaluating therapeutic approaches to peri-implant diseases, in terms of reporting, outcome measurements, and methods?	Treatment of peri-implantitis	High
Heitz-Mayfield et al[31]	In patients with osseointegrated implants diagnosed with peri-implantitis, how successful is treatment aimed at resolution of the disease?	Treatment of peri-implantitis	High
Khoshkam et al[32]	1. Do reconstructive surgical procedures provide beneficial clinical outcomes in comparison with other surgical techniques (resective surgeries and open flap debridement) in the treatment of peri-implantitis? 2. What are the overall treatment outcomes of reconstructive procedures in treating peri-implantitis?	Treatment of peri-implantitis	High
Khoshkam et al[33]	How do the effects of regenerative treatment of peri-implantitis compare to those of other treatment modalities, such as open-flap debridement, after a minimum healing time of 36 months in human subjects?	Treatment of peri-implantitis	High

TABLE 1
Continued

Study	Focused Question/Aims	Data Reported	AMSTAR Rating
Kotsakis et al[34]	Is laser therapy, as a monotherapy or as an adjunctive therapy, an efficacious treatment modality for patients with peri-implantitis?	Treatment of peri-implantitis	High
Kotsovilis et al[35]	To evaluate the efficacy of all treatment modalities implemented for the therapy of peri-implantitis	Treatment of peri-implantitis	High
Mahato et al[36]	What is the recommended treatment for management of peri-implantitis?	Treatment of peri-implantitis	Medium
Monje et al[37]	What is the impact of peri-implant maintenance therapy upon the incidence of biologic complications (ie, mucositis and peri-implantitis)?	Prevalence of peri-implantitis	High
Muthukuru et al[38]	To evaluate the clinical efficacy and safety of non-surgical therapy in the treatment of peri-implantitis	Treatment of peri-implantitis	Medium
Natto et al[39]	To investigate different types of laser therapy in surgical and non-surgical treatment of peri-implantitis	Treatment of peri-implantitis	High
Padial-Molina et al[40]	What are the microbial profiles of human patients suffering peri-implantitis in comparison to healthy implants?	Microbial findings for peri-implantitis	Medium
Perez-Chaparro et al[41]	Is there any evidence of differences in the subgingival microbial composition of healthy implants and implants with peri-implantitis present in independent patients?	Microbial findings for peri-implantitis	High
Rakic et al[42]	To qualitatively estimate the microbiologic profile associated with peri-implantitis in humans	Microbial findings for peri-implantitis	High
Ramanauskaite et al[43]	Is there a relationship between history of chronic periodontitis and dental implant success (used marginal bone loss beyond biological bone remodeling [eg, more than 2 mm] at baseline and final follow-up examination as the assessment criteria) and survival rates (defined as the presence of retained implants over the observation period)	Prevalence of peri-implantitis	Medium
Ramanauskaite et al[44]	What is the effectiveness of nonsurgical and surgical treatment methods for clinical and radiographic peri-implantitis symptoms resolution with respect to probing depth, bleeding on probing, and marginal bone loss?	Treatment of peri-implantitis	Medium
Sahrmann et al[45]	To systematically evaluate the outcome of GBR using a bone graft substitute in combination with a membrane to treat bone defects derived from peri-implantitis on the basis of the parameters PPD, BOP, and marginal bone loss	Treatment of peri-implantitis	Medium
Schwarz et al[46]	In patients with peri-implant mucositis and peri-implantitis, what is the efficacy of nonsurgical (ie, referring to peri-implant mucositis and peri-implantitis) and surgical (ie, referring to peri-implantitis) treatments with alternative or adjunctive measures on changing signs of inflammation compared with conventional nonsurgical and surgical treatments alone?	Treatment of peri-implantitis	High
Sgolastra et al[47]	Can smoking be considered a risk factor for peri-implantitis?	Prevalence of peri-implantitis	High
Sousa et al[48]	What are the survival and success rates (including bone-level change or bone loss) and incidence of peri-implantitis for dental implants placed in partially dentate patients who have been treated for periodontitis (treated periodontitis) compared with patients without a history of clinical or radiographic evidence of periodontitis (non-periodontitis)?	Prevalence of peri-implantitis	High

Table 1
Continued

Study	Focused Question/Aims	Data Reported	AMSTAR Rating
Suárez-lópez del Amo et al[49]	In patient suffering from peri-implant mucositis or peri-implantitis, what is the effectiveness of non-surgical therapy by means of different techniques and or approaches for clinical and radiographically resolution of disease, including BOP, PPD, and radiographic bone level changes?	Treatment of peri-implantitis	High
Tseng et al[50]	To determine if there is an associated risk of peri-implantitis in patients with diabetes	Effect of systemic disease on peri-implantitis	High
Turri et al[51]	In patients with osseointegrated dental implants, does the presence of smoking habits or a compromised medical status influence the occurrence of peri-implantitis compared with the presence of good general health?	Effect of systemic disease on peri-implantitis	Medium
Zangrando et al[52]	What are the long-term outcomes of periodontitis patients submitted to periodontal therapy/ maintenance and implant placement? Can the original periodontal diagnosis influence the implant prognosis?	Prevalence of peri-implantitis	High

*AMSTAR indicates Assessment of Multiple Systematic Reviews; GBR, guided bone regeneration; PPD, probing pocket depth; BOP, bleeding on probing.

Science, 19 from the Cochrane Library, 64 from Google Scholar, and 14 from hand searching of the reference list of the selected systematic reviews or meta-analyses. The duplicates were eliminated and a total of 83 reviews remained for full-text analysis. After full-text analysis, 50 were eliminated, resulting in 33 selected for data extraction (Figure 1).

Of the 33 articles selected,[20–52] 8 reviewed prevalence, incidence, or risk of peri-implantitis,[20,23,24,37,43,47,48,52] 2 reviewed diagnostic findings,[25,29] 3 reviewed microbial findings,[40–42] 2 reviewed the effects of systemic disease,[50,51] and 18 reviewed treatment interventions.* The AMSTAR ratings of the selected studies consisted of 24 reviews of high quality and 9 reviews of moderate quality (Table 1).

Prevalence, incidence, or risk of peri-implantitis

A total of 8 reviews reported on the prevalence, incidence, and risk of peri-implantitis (Table 2). Six of the 8 reviews reported on the prevalence or incidence of peri-implantitis in patients with chronic periodontitis or a history of periodontitis.[20,23,37,43,48,52] Three out of 8 reviews reported on prevalence or incidence of peri-implantitis in smokers and non-smokers.[20,23,47] However, the conclusion drawn from these systematic reviews was based on significant heterogeneity among most of the studies reviewed.

Based on a computed overall summary estimates, the frequency of patients with peri-implantitis was 18.8%, and the frequency of implants with peri-implantitis was 9.6%.[20] Another review reported that the prevalence of peri-implantitis ranged from 1%–47% with an estimated weighted mean prevalence of 22%.[24] Figure 2 showed differences in reported prevalence ranges on a patient level compared to on an implant level, in the same patient population.[20,23,24,37] Peri-implantitis was less likely to occur during the first 5 years of implant function; implants affected by peri-implantitis ranged from 0–3.4%.[23] After an observation period of 10 years, implants affected by peri-implantitis ranged from 10.7%–47.2%.[23] Thus, after the first 5 years, peri-implantitis was a frequently observed problem. With patients who were enrolled in supportive maintenance programs, the frequency of patients with peri-implantitis decreased to 14.3%.[20] A minimum implant recall interval of 5 to 6 months was suggested for a significant positive impact on the incidence of peri-implantitis.[37]

A majority of the reviews reported significantly lower occurrence of peri-implantitis in non-periodontitis patients compared with periodontitis patients.[20,23,37,43,48] Implants placed in patients with a history of treated periodontitis [43,48,52] reported wider ranges and higher percentages of peri-implantitis prevalence (Figure 3). Patients with a history of periodontitis also have a higher incidence of marginal bone loss around implants and peri-implantitis compared to non-periodontitis patients.[43] A higher incidence of peri-implantitis was also observed in generalized aggressive periodontitis at 26% compared to non-periodontitis patients at 10%.[48] Patients with residual pockets have more implant sites with peri-implantitis when compared to patients without residual pockets.[52]

A higher prevalence of peri-implantitis was reported in smokers.[20,23] An implant-based analysis revealed significantly greater risk of peri-implantitis in smokers compared to non-smokers.[47] However, the patient-based analysis conducted by the same systematic review did not find significant difference in peri-implantitis risk.[47]

Diagnostic findings for peri-implantitis

Two systematic reviews[25,29] reported on the effects of peri-implantitis on the levels of specific proinflammatory or anti-inflammatory cytokines (Table 3). There were higher levels of proinflammatory cytokines in the peri-implant crevicular fluid of implants with peri-implantitis than in healthy implants.[25,29]

* *References 21, 22, 26–28, 30–32, 34–36, 39- 44–46, 49.*

TABLE 2

Prevalence and incidence of peri-implantitis*

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Atieh et al[20]	Inclusion: • peri-implantitis defined as the presence of inflamed mucosa with a positive BOP, PD >5 mm, and cumulative bone loss of >2 mm and or >3 threads of implant • human study in English • prospective, retrospective, cross-sectional, and observational cohort study reporting the number of cases of peri-implant mucositis and or peri-implantitis • follow-up duration of at least 5 years of functional loading time • in multiple publications of the same study, the most detailed information was included Exclusion: • case series or case reports • clinical parameters to define peri-implant diseases not clearly define • failed to report the number of implants with peri-implant diseases • had an observation period of <5 years after functional loading Quality: • quality assessment tool derived from the STROBE statement[53] was developed to assess the quality of reporting of the studies	• at the participant level, the computed overall summary estimates of the frequency of peri-implantitis was 18.8% • at the implant level, the summary estimates for the frequency of peri-implantitis was 9.6% • the frequency of peri-implantitis in participants with previous periodontitis was 21.1% • frequency of participants with peri-implantitis was significantly higher among smokers at 36.3% • participants who were enrolled in supportive maintenance programs, the frequency of peri-implantitis was reduced to 14.3%
de Waal et al[23]	Inclusion: • peri-implantitis was defined as presence of inflammation in the peri-implant mucosa, as indicated by bleeding and/or pus on probing, with loss of supporting bone[6] • prospective studies with follow-up periods of at least 5 years or cross-sectional studies with implants in function for at least 5 years • studies combining data on subjects with 5-year follow-up and data on subjects with shorter follow-up periods only if a breakdown of data corresponding to 5 years of observation • studies reporting on fully edentulous subjects and or partially edentulous subjects who were treated with implant-supported reconstructions • treatments with titanium endosseous implants Exclusion: • retrospective studies • studies were excluded if <5 patients were evaluated at the final examination • studies not reporting on dental status or not allowing for breakdown of data corresponding to dental status • studies evaluating implant therapy in specifically selected subsets of patients, for example diabetes • ceramic, submucosal, blade, transmandibular, and zygoma implants • studies evaluating immediate implant placement Quality: • quality assessed using the quality assessment tool developed by den Hartog et al[54] • studies scoring 5 or more "plusses" were considered methodologically "acceptable"	• peri-implantitis prevalence reported on implant level ranged from 0% to 3.4% after an observation period of 5 years and from 5.8% to 16.9% after an observation period of 10 years • prevalence of peri-implantitis on subject level ranged from 10.7% to 47.2% after 10 years of observation • peri-implantitis is not very likely to occur within the first 5 years of implant functioning, whereas after this period it is a frequently observed problem • a higher prevalence is reported in smokers and patients with a history of periodontitis

The studies included in both systematic reviews were heterogeneous regarding the diagnosis of peri-implantitis. IL-1β release and TNF-α release was significantly higher in peri-implantitis compared to healthy peri-implant mucosa.[25,29] However, the IL-1β levels in peri-implantitis was not statistically significant when compared to peri-implant mucositis.[29] Increased levels of IL-1β and TNF-α in peri-implant crevicular fluid from sites with peri-implantitis have been related to increased gingival index, probing depth, bleeding on probing, and bone loss.[29] Other cytokines like IL-4, IL-6, IL-8, IL-10, IL-12, and IL-17 have also been investigated for a link to peri-implantitis. These proinflammatory or anti-inflammatory cytokines associated

Table 2
Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Derks and Tomasi[24]	Inclusion: • studies evaluating the incidence or prevalence of peri-implant mucositis and peri-implantitis • prospective longitudinal studies, cross-sectional studies and no limits were applied in regard to minimum function time of the implants • only studies reporting on at least 100 subjects • subject-level data Quality: • the assessment of quality of reporting according to the STROBE[53] checklist • adherence to the STROBE criteria varied between 55% and 77% • risk of bias is not assessed	• the prevalence of peri-implantitis ranged from 1% to 47% • estimated weighted mean prevalence for peri-implantitis was 22% • heterogeneity across studies was high and the reported results should be interpreted with caution
Monje et al[37]	Inclusion: • prospective or retrospective, randomized or not, cohort or case series trials involving human subjects • rough surface implant • >10 subjects and > 6 mo follow-up Exclusion: • systematic reviews, animal trials, case reports, in vitro studies Quality: • the 13 included studies scored a mean of 5.30 + 1.32 on the Newcastle–Ottawa scale	• a history of periodontal disease has significant effects on the incidence of peri-implantitis at both implant and patient levels • mean peri-implant maintenance therapy interval was demonstrated to reduce the incidence of peri-implantitis at implant but not patient level • these findings suggest a minimum recall peri-implant maintenance therapy interval of 5 to 6 mo due to the significant positive impact on incidence of peri-implantitis
Ramanauskaite et al[43]	Inclusion: • peri-implantitis defined as continuous marginal bone loss beyond biological bone remodeling (eg, more than 2 mm) and with signs of inflammation (eg, purulent, bleeding on probing, and more than 6 mm probing pocket depth) • prospective, retrospective cohort, cross-sectional studies reporting on outcomes of peri-implantitis and/or implant survival and/or peri-implant bone loss in patients with and without a history of periodontitis • studies with at least 5-year follow-up • studies with at least 10 patients • smokers were not excluded • use of titanium endosseous implants • studies restricted to English Exclusion: • aggressive periodontitis, case reports and systematic reviews	• majority of reviewed studies reported statistically lower occurrence of peri-implantitis in non-periodontitis patients compared with periodontitis patients • chronic periodontitis was found to be statistically significantly associated with higher prevalence of peri-implantitis • history of chronic periodontitis was associated with higher incidence of peri-implantitis • patients with history of periodontitis had higher incidence of having more implant marginal bone loss and peri-implantitis when compared with non-periodontitis patients • there was significant heterogeneity among studies
Sgolastra et al[47]	Inclusion: • prospective cohort studies that compared smoking with nonsmoking patients and reported data on the incidence of peri-implantitis Exclusion: • case series, reviews, non-longitudinal cross-sectional studies, case reports, and retrospective studies Quality: • none of the included studies reached the maximum score of the Newcastle–Ottawa Scale[55]	• with no evidence of heterogeneity, the patient-based analysis did not reveal any significant difference between smokers and nonsmokers for risk of peri-implantitis • with no evidence of heterogeneity, the implant-based analysis revealed a higher and significant risk of peri-implantitis in smokers compared with nonsmokers

with peri-implantitis increased with peri-implant establishment and progression.[29]

Microbial findings for peri-implantitis

Three systematic reviews[40–42] reported on the microbial findings in peri-implantitis (Table 4). The microbiologic profile of peri-implantitis is different from periodontitis and can be complex and variable.[42] It consists of aggressive and resistant microorganisms and may include opportunistic microorganisms, gram-negative anaerobic pathogens, gram-positive non-saccharolytic anaerobic rods, and Epstein–Barr virus. Although conflicting results have been reported, the following microorganisms were found to be more prevalent in peri-implantitis[40,41] than in peri-implant health: *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella*

TABLE 2
Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Sousa et al[48]	Inclusion: • peri-implantitis was defined as an incidence of probing pocket depth ≥5mm with BOP and or suppuration and radiographic signs of bone loss of ≥2.5 mm or bone loss extending ≥ the first 3 threads[16] • all other definitions of peri-implantitis were also included[11,15,65] • all longitudinal studies, RCTs, controlled clinical trials, cohort studies, case control studies and case series reporting on titanium dental implant survival and or success • for RCTs, single arms (subgroup) of studies that presented data separately for treated periodontitis and non-periodontitis patients • studies reporting on implants with at least 6 months of loading • studies including partially dentate periodontal patients who received periodontal treatment with a comparison group of patients without a history of periodontitis • studies including at least 10 patients • studies on smokers • studies presenting a different type and or severity of periodontitis • periodontal treatment was defined as the non-surgical/surgical treatment undertaken by a suitably trained dentist or dental auxiliaries Exclusion: • individual case reports • studies that evaluated specifically at medically compromised individuals Quality: • the methodological quality assessment of the included studies was adapted from the Newcastle–Ottawa scale • study quality scores ranged from a total of 7 to a total of 9 (of a maximum total of 9 stars)	• incidence of peri-implantitis was lower in the non-periodontitis patients in comparison with the patients with treated periodontitis, a statistically significant difference was reported in some studies • incidence of peri-implantitis was also higher in the severe periodontitis group (3.1% to 66.7%), as compared with the moderate periodontitis group (0–66.7%) and with the non-periodontitis group (0–18.8%) of the 3 included studies that reported periodontal disease severity and in relation to this outcome over a 5- to 10-year follow-up period • a higher incidence of peri-implantitis was also reported in generalized aggressive periodontitis patients at 26% as compared with a non-periodontitis group at 10% • within the limits of this systematic review, it may be concluded that biological complications of dental implants increase in patients with history of periodontitis • the lack of supportive periodontal therapy and the presence of smoking may negatively influence the implant outcomes
Zangrando et al[52]	Inclusion: • peri-implant PD >5 mm with BOP was used as a threshold to define peri-implantitis • observational studies, randomized controlled trials, and or controlled clinical trials • studies reported outcomes from titanium implants placed in partially edentulous patients with a history of treated periodontitis • evidence that patients with periodontitis had undergone active periodontal treatment and/or maintenance therapy for >5 years Exclusion: • studies not reporting that patients with periodontitis received periodontal therapy before implant placement and periodontal maintenance after implant placement Quality: • methodologic quality of observational studies was evaluated with the assistance of an adapted version of the Newcastle–Ottawa scale • most of the included studies (77.8%) presented a medium/high methodologic quality	• there were more implant sites with peri-implantitis in the RP subgroup than in the NRP subgroup • statistical analysis from individual studies suggest that implant therapy can be successfully used in patients with a diagnosis of periodontitis, as long as the periodontitis is properly treated and the patient adheres to the periodontal maintenance program • the presence of RPs and non-attendance to periodontal maintenance observed during the follow-up period and smoking habit can be considered negative factors for implant outcomes

*BOP indicates bleeding on probing; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; PD, probing depth; RCT, randomized controlled trials; RP, residual pocket; NRP, non-residual pocket.

intermedia, and *Treponema denticola,* human herpesvirus 4 and 5, Epstein–Barr 1, and human cytomegalovirus 2.[40] In addition, microorganisms such as *Tannerella forsythia*, *Porphyromonas gingivalis*, *Treponema socranskii*, *Staphylococcus aureus*, *Staphylococcus anaerobius*, *Staphylococcus intermedius*, and *Streptococcus mitis* were also found comprising 30% of the total microbiota at peri-implantitis sites.[40] Peri-implantitis sites have higher mean colony-forming units in peri-implantitis sites

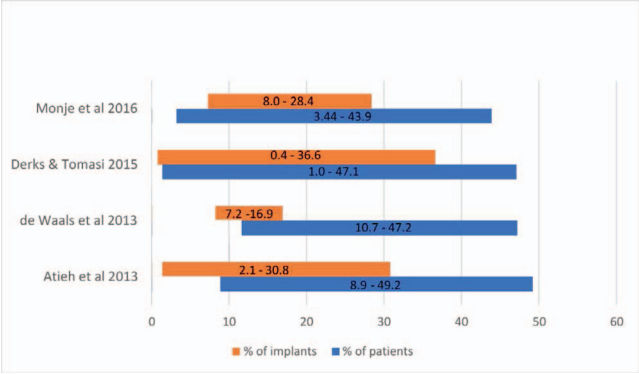

Figure 2. Ranges of peri-implantitis prevalence reported in selected systematic reviews.

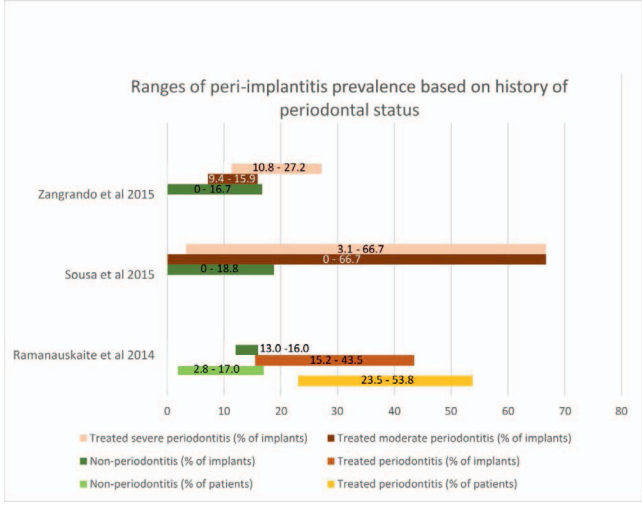

Figure 3. Ranges of peri-implantitis prevalence reported in selected systematic reviews based on history of periodontal status.

compared with healthy sites.[42] The reported active periodontal pathogens are not limited to periodontopathic bacteria, and can include opportunistic bacteria like *Staphylococcus aureus*, *Staphylococcus intermedius*, *Streptococcus mitis*, and *Haemophilus influenzae*.[42]

Effects of systemic disease on peri-implantitis

Two systematic reviews[50,51] reported on the effects of systemic diseases on peri-implantitis (Table 5). Patients with diabetes were at a higher risk of peri-implantitis.[51] The gingival index, probing depths, and bone loss were higher in poorly controlled compared to well-controlled diabetic peri-implantitis patients.[50] However, conflicting results were reported for type 2 diabetes.[50]

Patients with cardiovascular disease were also at a higher risk of peri-implantitis.[50] In addition, patients with peri-implantitis were found to have a 3 times greater chance of harboring Epstein–Barr virus.[50] However, for patients with rheumatoid arthritis, statistical analysis demonstrated no associations.[50]

Treatment of peri-implantitis

A total of 18 reviews[†] reported on the non-surgical and surgical interventions to treat peri-implantitis (Table 6). Non-surgical interventions focused on implant surface treatment and detoxification, with or without the use of an anti-microbial agent. The non-surgical interventions included manual debridement, manual debridement with chlorhexidine, ultrasonic debridement, air-abrasive device, local or systemic antibiotics, local antiseptic application, lasers, and host modulation therapy. Non-surgical therapy is most effective at removing only the local irritant from peri-implantitis and is not helpful in osseous defects.[36,49]

Surgical interventions focused on flap elevation, implant surface treatment, and detoxification, with or without the use of an anti-microbial agent, and with or without the use of membranes or grafting materials. The surgical treatments included (1) open-flap debridement with plastic or carbon curettes, ultrasonic scaler, rotating instruments, air powder, or soft laser treatment; (2) resective peri-implant surgery and implantoplasty; and (3) guided bone regeneration techniques with or without different types of membranes (synthetic membranes, resorbable bovine or porcine collagen) in combination with or without bone substitutes (demineralized freeze dried bone alone or in combination with growth factors, autogenous bone, hydroxyapatite, xenografts, and algae-derived calcium carbonate).

Various adjunctive therapies may improve the efficacy of conventional peri-implantitis treatment.[46] Debridement together with antibiotics resulted in the greatest probing depth reduction compared to debridement only.[28] At a short-term follow-up of 12 months, mechanical debridement and minocycline appeared to improve treatment outcomes of peri-implantitis when compared to debridement and chlorohexidine.[35,38] The use of erbium: yttrium–aluminum–garnet (Er:YAG) laser and carbon dioxide (CO^2) lasers can improve short-term implant clinical parameters up to 6 months.[35,39] Er:YAG laser treatment may also result in greater reduction in bleeding on probing (BOP) scores compared with submucosal debridement with adjunctive submucosal irrigation with chlorhexidine.[35,38] Implantoplasty or lasers might provide equivalent effects when compared to other commonly used methods for surface decontamination.[21] In addition, the use of submucosal glycine powder air polishing may greatly reduce BOP scores compared to submucosal irrigation with chlorhexidine digluconate and debridement; and produced similar clinical outcomes compared with Er:YAG laser treatment.[38] Network meta-analysis of other non-surgical approaches in peri-implantitis treatment showed that single or combined non-surgical interventions also resulted in greater probing depth reduction than debridement alone.[28]

In short-term follow-ups, surgical interventions reduced probing depth by 30%–50% of the initial probing depth.[21,32] Although regenerative procedures can achieve a mean of 2–2.41 mm radiographic bone fill,[21,32,33,44] and can improve clinical parameters of peri-implant tissues,[22,44] the use of a guided bone regeneration protocol with membrane and bone graft does not seem to be predictable in treatment of peri-

[†] *References 21, 22, 26–28, 30–32, 34–36, 38, 39, 44–46, 49.*

TABLE 3

Diagnostic findings for peri-implantitis*

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Duarte et al[25]	Inclusion: • original studies published in English • studies comparing the protein levels of cytokines in the PICF around healthy implants with those in the PICF around implants with peri-implantitis Exclusion: • abstracts, animal studies, in vitro studies, case reports, case series, letters to the editor, and reviews • studies that evaluated only biomarkers recognized as receptors, hormones, enzymes, antioxidant agents, reactive oxygen species, antimicrobial peptides, antibodies, inorganic ions, platelet-activating factor, arachidonic acid metabolites, growth factors and adhesion molecules, as well as subsets of cells • studies that evaluated cytokines in tissue, serum, saliva, and other biological sources Quality: • not assessed	• implants with peri-implantitis present higher levels of proinflammatory cytokines in the peri-implant crevicular fluid than healthy implants • most studies reported higher levels of IL-1β, IL-6, IL-17, and TNF-α in implants with peri-implantitis than in healthy implants • studies reported conflicting results for RANKL and IL-10 in peri-implantitis and healthy implants • studies reported no difference in concentrations of IL-4, IL-8, and IL-12 in implants with peri-implantitis than in healthy implants
Faot et al[29]	Inclusion: • original cross-sectional and longitudinal prospective clinical studies with collection of proinflammatory cytokines in PICF from individuals with PP or MU peri-implants • studies had to analyze protein expression by ELISA or flow cytometry using a cytometric bead array system • reports in English Exclusion: • animal and in vitro studies, letters to the editor, case reports, and reviews • studies with quantification of proinflammatory ILs in tissue biopsies • analysis of osteogenic markers and histamine • assessment of fluid volume but not cytokine levels • fluid collection during early osseointegration • focus on gingival distances • unreported implant failure criteria • exclusively on the effects of smoking Quality: • not assessed	• statistical differences were observed when the IL-1β release was compared between healthy and PP; and when PP and MU conditions were compared, no statistical differences were found • for TNF-α release, significant differences were found between healthy and PP conditions • increased GI, PD, BOP, and bone loss have been related with increased levels of IL-1β and TNF-α in PICF from sites with PP • other cytokines IL-4, IL-6, IL-8, IL-10, IL-12, and IL-17, were also linked to PP • the level of these specific proinflammatory or anti-inflammatory cytokines rise with PP establishment and progression • great heterogeneity was observed regarding the PP diagnosis

*PICF indicates peri-implant crevicular fluid; RANKL, receptor activator of nuclear factor kappa-B ligand; IL-1β, interleukin-1 beta; IL-6, interleukin 6; IL-17, interleukin 17; TNF-α, tumor necrosis factor alpha; IL-10, interleukin 10; IL-4, interleukin 4; IL-8, interleukin 8; IL-12, interleukin 12; PP, peri-implantitis; MU, mucositis; ELISA, enzyme-linked immunosorbent assay; ILs, interleukins; GI, gingival index; PD, probing depth; BOP, bleeding on probing.

implantitis.[21,22,33,45] When all surgical and non-surgical approaches were pooled together, surgical approaches showed greater improvements in probing depth and clinical attachment levels. However, when the surgical and non-surgical approaches were analyzed separately, the difference between the approaches were not statistically significant.[27]

Successful treatment outcomes of peri-implantitis were described as post-treatment implants with a mean probing depth of less than 5 mm and no progressing bone loss. At 12 months' follow-up, Heitz-Mayfield et al[31] reported successful overall peri-implantitis treatment outcomes for different combinations of adjunctive treatments for surgical and non-surgical interventions at 76%–100% of patients, and at 75%–93% of implants.

DISCUSSION

This overview had only included systematic reviews of medium to high quality, and the majority of the systematic reviews reviewed in this overview were of high quality in terms of the conduct of the systematic review according to the AMSTAR rating[19] (Table 1). However, the conclusions derived from most of the peri-implantitis systematic reviews needed to be interpreted with caution as stated by the individual systematic reviews included in the overview. In general, the included systematic reviews had the following limitations inherent in their selected studies: variation of the study designs, different implant systems used, and varying duration of follow-up periods, as well as the lack of standardization in reported outcomes at participant and implant levels. Other limitations were from the inability to control co-existing confounding factors in the pre-existing studies, and from restricting the search to English, as studies published in other languages were overlooked.

Furthermore, the definition used for peri-implantitis was different across studies and all variations of peri-implantitis definitions were included in this overview. The following are the different definitions of peri-implantitis used by the selected

TABLE 4

Microbial findings for peri-implantitis*

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Padial-Molina et al[40]	Inclusion: • studies on humans published in the English language • at least 1 osseointegrated titanium screw-shaped dental implant with signs of peri-implantitis or peri-implant mucositis, with or without healthy implants or teeth • studies had to have clear implant status definition for the conditions health, mucositis and or peri-implantitis and analyze the microbiome of those situations, with or without comparisons among them or with or without before and after results Exclusion: • letters, editorials, case reports, literature reviews, and PhD theses • animal or in vitro studies, not enough information on the microbial analysis, analysis not performed on peri-implant sulcus of dental implants aimed at supporting restorations, and no access to the abstract or full text Quality: • risk of bias within articles was assessed • most of the included studies on this topic contain a moderate risk of bias	• different detection methods prevent comparisons between studies • when using culture techniques, 1 study found significantly higher prevalence of *Porphyromonas*, *Prevotella,* and anaerobic Gram-positive cocci in peri-implantitis compared to peri-implant health • when using PCR techniques, conflicting results were reported in the detection frequencies of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia,* and *Treponema denticola* between healthy and diseased implants • when using PCR techniques, studies reported differences for *Tannerella forsythia*, *Fusobacterium nucleatum*, *Peptostreptococcus micros*, *Campylobacter rectus*, *Eikenella corrodens*, *Candida albicans*, *Prevotella nigrescens*, *Centruroides gracilis*, *Capnocytophaga ochracea*, *Campylobacter concisus*, *Streptococcus spp*., *Actinomyces odontolyticus*, *Veillonella parvula,* and *Enterococcus faecalis* between healthy and diseased implants • when using checkerboard DNA–DNA technique, one study found a cluster of *T. forsythia*, *P. gingivalis*, *Treponema socranskii*, *Staphylococcus aureus*, *Staphylococcus anaerobius*, *Staphylococcus intermedius*, and *Streptococcus mitis* that comprised 30% of the total microbiota at peri-implantitis sites • when using the 16S rRNA gene sequencing technique, 1 study found a 10-fold higher mean colony-forming units in peri-implantitis sites compared to healthy implant sites, with periodontopathic bacteria not being the only periodontal pathogens active in peri-implantitis
Perez-Chaparro et al[41]	Inclusion: • systematically healthy patients • studies comparing subgingival peri-implant microbiota from healthy implants and implants with peri-implantitis • peri-implantitis defined as the presence of probing depth $\geq$4 mm with BOP and or SUP and radiographic bone loss • implants in prosthetic function for at least 1 year Exclusion: • studies published in languages other than English, Spanish, Portuguese, or French • samples from healthy implants collected from periodontitis patients • studies that did not report period of prosthetic function • reviews studies, case report, and letter to the editor • studies evaluating peri-implant mucositis only Quality: • not assessed	• the microorganisms found in increased counts or frequency in peri-implantitis included a total of 6 bacterial phyla, 17 bacterial genera, 23 bacterial species, and 2 genera of viruses • 1 study reported higher frequency of *Porphyromonas* sp., *Prevotella intermedia*, *Tannerella forsythia*, *Treponema denticola,* and *Aggregatibacter actinomycetemcomitans* in peri-implantitis than in healthy implants • another study did not find any difference between the frequency of detection of 10 bacterial species between healthy implants and implants with peri-implantitis • 5 studies observed increased counts/frequency of species belonging to the phylum *Bacteroides*, including *Porphyromonas* species, *P. intermedia,* and *T. forsythia*, 3 of these 5 studies also reported higher counts/frequency of species belonging to the phylum *Spirochaetes*, including *Treponema* species • 2 studies reported human herpesvirus 4 and 5 as well as the genotypes Epstein–Barr 1 and human cytomegalovirus 2 were found in higher prevalence in peri-implantitis compared to healthy implants • there is "Moderate Evidence" to support the association of *P. gingivalis*, *T. denticola,* and *T. forsythia*, and "Some Evidence" to support the association of *P. intermedia* and *C. rectus* with the etiology of peri-implantitis

Table 4

Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Rakic et al[42]	Inclusion: • randomized clinical trials, prospective cohort studies, case control studies, and cross-sectional studies in humans reporting microbiologic findings in patients diagnosed with peri-implantitis • peri-implantitis was defined as the radiographic presence of bone loss >2 mm since the time of prosthetic replacement, positive bleeding on probing, and probing depth >5 mm • studies published in English Exclusion: • in vitro and animal studies and studies of blade implants Quality: • quality assessed per Khan et al[61]	The microbiologic profile of peri-implantitis consists of aggressive and resistant microorganisms and is distinct from that of periodontitis The microbiologic profile in peri-implantitis: 1. is complex and variable 2. consists of gram-negative anaerobic periopathogens and opportunistic microorganisms in almost the same ratio 3. is frequently associated with Epstein–Barr virus and nonsaccharolytic anaerobic gram-positive rods 4. is not so strictly associated with *Staphylococcus aureus* 5. is different from that of periodontitis

*PCR indicates polymerase chain reaction; BOP, bleeding on probing; SUP, suppuration; rRNA, ribosomal ribonucleic acid.

systematic reviews: (1) the consensus definition agreed upon in the 1st European Workshop on Periodontology,[15] (2) the presence of inflammation in the peri-implant mucosa, as indicated by bleeding and or pus on probing, with loss of supporting bone,[6] (3) a continuous marginal bone loss beyond biological bone remodeling or more than 2 mm; and with signs of inflammation like purulence, bleeding on probing, and more than 6 mm probing pocket depth, (4) an incidence of probing pocket depth ≥5 mm with bleeding on probing and or suppuration and radiographic signs of bone loss of ≥2.5 mm or

Table 5

Effects of systemic diseases on peri-implantitis

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Tseng et al[50]	Inclusion: • cohort, case controlled, and cross-sectional studies • human study population Exclusion: • case reports, reviews • animal studies, in vitro, or experimental studies • studies without qualitative analysis of the risks of diabetes on peri-implantitis Quality: • quality assessments were conducted according to the guidelines of the Agency for Healthcare Research and Quality[62]	• based on the pooled odds ratios between patients with and without diabetes, patients with diabetes are at a higher risk of peri-implantitis • caution should be observed when implants are placed in patients with diabetes • cautionary measure would include ensuring an excellent degree of glycemic control, supportive periodontal treatment, and a well-designed peri-implant maintenance plan
Turri et al[51]	Inclusion: • prospective and retrospective cohort studies, case control studies, cross-sectional surveys, and case series • human trials with a minimum of 10 subjects and a mean time of functional loading of the implants of at least 1 year • studies published in English • systemic conditions or diseases such as type 2 diabetes, cardiovascular diseases, rheumatoid arthritis, lung diseases, obesity, cancer, deep depression, osteoporosis, Epstein–Barr virus, and smoking Quality: • quality assessment of selected studies was performed using the Cochrane tool (for randomized trials) and or the Newcastle–Ottawa scale for cohort studies • the Newcastle–Ottawa scale is composed of three sections: selection, comparability, and outcome • none of the studies reached the maximum score for selection and comparability items • all selected studies reached the maximum score for outcome	• modified gingival index, probing depths, and bone loss was higher in poorly controlled versus well-controlled diabetic peri-implantitis patients • another study found no association between peri-implantitis and type 2 diabetes • based on the odds ratio, patients with cardiovascular disease are at an increased risk of peri-implantitis • for rheumatoid arthritis, statistical analysis demonstrated no associations • patients with peri-implantitis were found to have a 3 times greater chance of harboring Epstein–Barr virus

Table 6

Treatment of peri-implantitis*

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Chan et al[21]	Inclusion: • included studies were human clinical trials comprising case series, cohort studies, quasi-experiments, and RCTs that were published in English • applied surgeries for treating peri-implantitis • reported on at least 1 clinical or radiographic parameter • had a minimum sample size of 8 implants • at least 3 months follow-up for surgical interventions other than regenerative procedures, which had a follow-up period of 6 months or more • screw-shaped implants with either smooth or rough surfaces • no restriction on the methods for surface detoxification used Exclusion: • animal studies, reviews, and case reports Quality: • criteria used to assess the quality of the selected RCTs were modified from the RCT checklist of the Cochrane Center[56] and the CONSORT statement[57] • 1 study was considered to have a low risk of bias, another 3 studies were considered to have a moderate risk of bias, and another study a high risk of bias	Characteristics of interventions: Surgical interventions: • access flap and debridement • surgical resection • regeneration with bone grafts • GBR Conclusions: • in short-term follow-ups, these procedures yielded an estimated 2- to 3-mm PD reduction, equivalent to 30% to 50% of the initial PD • mean 2 mm radiographic bone fill was achieved with regenerative procedures • the number of included papers for each surgical procedure is low, and only some studies compared treatment effects of different surgical approaches • various degrees of heterogeneity in the study design, case selection, and treatment provided among studies • the regenerative procedures using bone graft materials in combination with barrier membranes might be more effective, but the outcomes of the regenerative procedures were also the most varied • due to small number of selected studies, comparisons among different bone grafting materials, membrane types, and healing protocols were not performed • limited evidence suggested that implantoplasty could improve clinical outcomes, and lasers might provide equivalent effects to other commonly used methods for surface decontamination
Daugela et al[22]	Inclusion: • included all human prospective and retrospective follow-up studies and clinical trials, cohort studies, case control studies, and case series published in English • subjects must have had at least 1 osseointegrated titanium screw-shaped dental implant with peri-implantitis • studies with a minimal sample size of 10 implants and at least 12 months follow-up after surgical regenerative treatment of peri-implantitis Exclusion: • animal studies, in vitro studies • implant risk-related systemic conditions like immunologic disorders, uncontrolled diabetes mellitus, or osteoporosis • ceramic or coated implants Quality: • Cochrane Collaboration's 2-part tool used for assessing risk of bias • most of the studies were classified as unclear risk • 2 studies were considered as having low risk of bias whereas another one was classified as moderate risk, and 3 studies were attributed to high risk of bias	Characteristics of interventions: Surgical regenerative interventions: • all included studies used grafting materials for peri-implant bone defect augmentation, with or without barrier membranes Conclusions: • surgical regenerative treatment is a predictable option in managing peri-implantitis and improving clinical parameters of peri-implant tissues • no fundamental advantage of membrane use for bone graft coverage or submergence of the healing site on the outcome of peri-implant defect regeneration

bone loss extending $\geq$ the first 3 threads,[16] (5) peri-implant probing depth $>$5 mm with bleeding on probing, (6) peri-implant crestal bone loss at osseointegrated dental implants in conjunction with inflammation of peri-implant mucosa.[17]

Another limitation to the systematic reviews was due to a lack of standardized assessment tools; there was a wide variation of unvalidated tools used to assess the quality of reporting of the selected studies; some were modified from validated assessment tools to evaluate the quality of non-randomized studies. The following were the quality assessment tools or criteria used by the selected systematic reviews of this overview to assess the quality of their included studies: (1) the

TABLE 6

Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Esposito et al[26]	Inclusion: • stable implants not surrounded by a radiographic radiolucent area • unspecified peri-implant bone loss • peri-implant bone loss exceeding 50% of the implant length Exclusion: • used antibiotics and anti-inflammatory prescription medications up to 3 months prior to the study • peri-implantitis treatment during the last 6 months or 12 months • mouth rinse with anti-inflammatory properties used up to 1 month prior to the study • mechanical debridement up to 3 months prior to the study • allergy to the tested antibiotics • <2 mm of keratinized mucosa • hollow cylinder implants • systemic diseases that could influence the outcome of the therapy, ie, diabetes, osteoporosis • presence of overhangs or margins • evidence of occlusal overload • presence of acute periodontitis • poor oral hygiene: plaque index >1 • heavy smokers (>10 cigarettes/day) Quality: • risk of bias assessment of the included trials using the recommended approach for assessing risk of bias in studies included in Cochrane reviews[56]	Characteristics of intervention: Different nonsurgical interventions: • local antibiotics versus ultrasonic debridement • air-abrasive device versus manual debridement • Er:YAG laser versus manual debridement with chlorhexidine subgingival application • Er:YAG laser versus air-abrasive device Adjunctive treatments to non-surgical interventions: • adjunctive local antibiotics versus manual debridement with chlorhexidine subgingival application Different surgical interventions: • augmentation with synthetic versus animal-derived bone substitutes • surface debridement with laser versus plastic curettes and saline solution before augmentation Adjunctive treatments to surgical interventions: • adjunctive implant surface smoothening versus systemic • antibiotics plus resective surgery plus 2 different local antibiotics Conclusions: • there is no reliable evidence suggesting which could be the most effective interventions for treating peri-implantitis • this is not to say that currently used interventions are not effective
Faggion et al[27]	Inclusion: • RCTs and CTs with 2 or more treatment groups related to peri-implantitis treatment in humans • no minimum follow-up time for the studies included Exclusion: • case series or reports, cross-sectional studies, animal studies, narrative and systematic reviews, consensus reports, expert opinion articles, letters, and editorials • potential studies published in other languages than those described in the "literature search process" • studies that did not present PPD and CAL as measure of outcomes were excluded from this review Quality: • assessed the risk of bias of RCTs by using components from the Cochrane tool described in the Cochrane Handbook for Systematic Reviews of Interventions • risk of bias of studies were either high or unclear	Characteristics of intervention: Nonsurgical interventions: • all types of treatment approaches without open-flap procedures, for example, implant scaling with curettes or other instruments and implant scaling plus adjunctive antimicrobial treatment with local disinfectants or antibiotics Surgical interventions: • open-flap procedures with implant scaling or implant scaling plus implant surface treatment or modification with or without any form of regenerative procedure (autogenous/substitute bone with or without membranes) Conclusions: • when all surgical approaches or nonsurgical ones were pooled together, surgical approaches showed greater changes in PPD and CAL than nonsurgical ones • when different surgical and nonsurgical approaches were treated separately, the differences became no longer statistically significant probably because of the small number of studies included • while network meta-analysis is a very useful tool for evidence synthesis for multiple intervention comparisons, the interpretation of its results still needs to consider the limitations in the study design and the methodology

tool derived from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement,[53] (2) the tool developed by den Hartog et al,[54] (3) the Newcastle–Ottawa scale[55] or an adaptation of it, (4) the tools modified from the randomized controlled trial checklist of the Cochrane Center[56] and or the Consolidated Standards of Reporting Trials (CONSORT) statement,[57] (5) the Risk of Bias tool from the Cochrane Collaboration,[56] (6) the tool from the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach,[58] (7) the modified criteria proposed by Esposito et al[59] and Roccuzzo et al,[60] (8) tool by Khan et al,[61] and (10) the criteria from the Agency for Healthcare Research

Table 6
Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Faggion et al[28]	Inclusion: • RCT in humans • non-surgical approaches for peri-implantitis therapy Exclusion: • other study designs, animal and in vitro studies • surgical approaches • duplicated data • RCTs without any intervention (eg, on prevalence) • RCTs with treatment outcomes other than CAL and PPD changes Quality: • studies were assessed using the ROB tool from the Cochrane Collaboration[56] • overall quality of evidence within the pair-wise meta-analysis was graded using the GRADE approach[58] • overall evidence was considered very low by the GRADE assessment • allocation concealment was the domain with highest ROB scores across the studies (9 from 11 assessments with high or unclear risk of bias) • the selective outcome reporting domain was considered with low ROB in all assessed trials	Characteristics of intervention: Nonsurgical interventions: • debridement (control), laser, debridement in conjunction with Periochip, the Vector system, air-abrasive powder, debridement in conjunction with antibiotics, photodynamic therapy, and debridement in conjunction with chlorhexidine gel Conclusions: • debridement in conjunction with antibiotics achieved the greatest additional PPD reduction in comparison to debridement only • the Vector system, debridement plus Periochip and photodynamic therapy have the highest probabilities of being the most effective interventions • systematic review and network meta-analysis on non-surgical approaches for treating peri-implantitis showed that various single and combined non-surgical therapies yielded greater PD reduction than debridement only • these results should be interpreted with caution due to the large credible intervals • the evidence does not conclusively show that any particular non-surgical treatment for peri-implantitis performs better than debridement alone
Graziani et al[30]	Inclusion: • studies had to be RCT or CCT assessing therapeutic and or preventive methods for peri-implant diseases • publications in English Exclusion: • cohort studies, case series, case reports, letters to editors, historical and systematic reviews Quality: • quality analysis of each RCT was performed according to the Cochrane Reviewers' Handbook[56] • the available scientific evidence on prevention and treatment of peri-implant diseases has limited quality	Characteristics of intervention: Nonsurgical interventions: • all control groups included scaling with different types of curettes either alone or with CHX as gel, irrigation and or rinse • test subgroup: mechanical debridement and the application of a local antibiotic submucosally, in the form of repeated doses of minocycline, a unique dose of minocycline, or irrigation with doxycycline • another test subgroup: a different debridement approach, an air-abrasive device, ultrasonic devices, or Er:YAG laser Surgical interventions: • the control group received the surgery with different decontamination procedures and or bone procedures (osteoplasty or grafting) • the test groups received additional membranes or implantoplasty • both control and test groups shared similar surgical and additional procedures, but different decontamination or regenerative approaches Conclusions: • this high level of heterogeneity were enhanced by the low number of retrieved articles • the quality of the published materials appeared insufficient to assess the validity of the trials • the low proportion of positively qualified items in the evaluation of the adequacy of methods and the high number of non-reported items, the literature examined in our review clearly indicated an inadequate protection from bias

and Quality.[62] The quality of the studies included in most of the systematic reviews were of high, moderate, or unclear risk of bias. Most studies were limited by an inadequate protection from bias leading to an insufficient quality to assess the validity of the trial.

The limitation of the peri-implantitis prevalence reviews (Figure 2) were that the studies reviewed did not factor in patients' age, systemic status, and history of periodontal status. This may account for the wide ranges reported for the % patients and % implants affected by peri-implantitis. In Figure 3, when the history of periodontitis was factored into the peri-implantitis prevalence. Lower ranges were reported in patients with healthy periodontium compared to patients with a history

TABLE 6

Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Heitz-Mayfield et al[31]	Inclusion: • reports with treatment outcomes evaluating nonsurgical or surgical interventions to treat peri-implantitis in humans • patients with at least one dental osseointegrated implant affected by peri-implantitis • clinical intervention treating peri-implantitis • at last 5 cases treated and followed up for at last 3 months after therapy Quality: • quality assessment and assessment of risk of bias conducted • majority of comparative studies were judged to be at unclear risk of bias, 2 studies were judged to have high risk of bias	Characteristics of interventions: Nonsurgical interventions: • implant surface treatment with/without adjunctive antimicrobials Surgical interventions: • implant surface treatment with/without adjunctive antimicrobials, with/without bone graft material, with/without barrier membrane Successful treatment outcome: • described as implant survival with mean PD <5 mm and no further bone loss • 11 studies presented data such that number of patients or implants with successful treatment outcome at 12 months could be determined • a majority of studies reported successful treatment outcomes at 76%–100% of patients • some studies reported successful treatment outcomes at 75%–93% of implants • a minority of studies reported none of the patients with a successful outcome
Khoshkam et al[32]	Inclusion: • randomized controlled trials, case series • at least 1 clinical and radiographic parameter between reconstructive therapies and other surgical modalities, such as resective or open-flap debridement surgeries, for treating peri-implantitis • a minimum sample size of 10 implants and at least 12 months of observation • studies that had performed implantoplasty in combination with reconstructive approach were also included • screw-shaped implants with either smooth or rough surface Quality: • risk of bias was assessed using criteria modified from the randomized clinical trial checklist of the Cochrane Center and the CONSORT statement • moderate risk of bias for randomized clinical trial	Characteristics of interventions: Surgical interventions: • implant surface treatment with bone grafting materials, including autografts, a combination of autografts and xenografts, allografts, xenografts, and others • nonresorbable and resorbable membranes, or no membranes were used • implants may or may not be submerged during the healing period Meta-analysis: • weighted mean radiographic defect fill was 2.17 mm • probing depth reduction was 2.97 mm • clinical attachment level gain was 1.65 mm • bleeding on probing reduction was 45.8% Conclusion: • no evidence to compare the clinical effectiveness of reconstructive and nonreconstructive procedures • no evidence to show that reconstructive procedures with the use of bone grafts and or membranes provide better treatment outcomes than nonreconstructive procedures
Khoshkam et al[33]	Inclusion: • human clinical trials published in English • >10 implants with 36 months follow-up and had reported at least 1 clinical or radiographic parameter for evaluation • screw-shaped implants with either smooth or rough surfaces Quality: • randomized controlled trials were assessed using the Cochrane Collaboration's tool for assessing risk of bias, the only included randomized controlled trial was reported as having low risk of bias • Newcastle–Ottawa scale was used to evaluate the methodological quality of nonrandomized studies, the selected nonrandomized studies were reported as having moderate to low risk of bias	Characteristics of interventions: Surgical interventions: Meta-analysis: Primary outcomes: • mean radiographic bone fill of 2.41 mm Secondary outcomes: • mean probing depth reduction of 3.06 mm • mean clinical attachment level gain of 1.76 mm • mean percentage of clinical attachment level gain of 26.4% • mean percentage of bleeding on probing reduction of 62.5% • mean mucosal level gain of 0.22 mm Conclusion: • Some of the studies reported that placing a membrane over the bone substitute did not improve long-term results, and after 36 months of follow-up there was no statistically significant difference in the amount of bone fill with or without a membrane • regenerative treatment of peri-implantitis resulted in a mean radiographic bone fill of 2.41 mm after a minimum healing time of 36 months

Table 6
Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Kotsakis et al[34]	Inclusion: • English language • human studies • prospective, controlled clinical studies reporting data from >10 patients • use of laser therapy as monotherapy or as an adjunct in the treatment of peri-implantitis • report of clinical indexes (or report of data allowing the calculation of clinical indexes) of peri-implant disease, including CAL and PD • follow-up of >6 months following treatment Quality: • clinical studies included in this study were assessed using criteria from the revised CONSORT statement • 3 of 6 studies have high risk of bias, 1 has moderate risk, and 2 have low risk	Characteristics of interventions: Nonsurgical and surgical interventions with: • Er:YAG laser treatment • CO_2 laser treatment • photodynamic therapy Meta-analysis: • relatively homogeneous inclusion/exclusion criteria for Er:YAG laser treatment at the 6-month post-intervention observation interval • the pooled effect sizes in AL after 6 months for the non-surgical group, the surgical group, and all studies were found to be non-significant • no statistically significant evidence for treatment effects in reducing PD level was found for the non-surgical group, surgical group, and all studies • there was no evidence for subgroup difference between surgical and non-surgical treatments in AL and PD reduction Conclusion: • based on the limited information currently available, any superiority of laser treatment in comparison to conventional treatment of peri-implantitis could not be identified
Kotsovilis et al[35]	Inclusion: • used the consensus definition agreed upon in the 1st European Workshop on Periodontology[15] • publication in the international peer-reviewed literature in the English language • randomized controlled or comparative (either of a parallel or of a split-mouth design) clinical trials • implementation of therapy for peri-implantitis (by any treatment modality • presence of at least 5 patients in each and every group of the study • follow-up period of at least 6 months Exclusion: • previous treatment of peri-implantitis over a period of 12 months before the initiation of the study • patients receiving antibiotics before the initiation of the study • history of radiotherapy in the head and neck region • absent or uncompleted periodontal therapy before dental implant placement • presence of active inflammation a the implant recipient site at the time of implant placement Quality: • quality assessed using a slight modification of the criteria proposed by Esposito et al[59] and Roccuzzo et al[60] • the risk of bias was estimated to be high for all selected studies	Characteristics of interventions: Nonsurgical interventions: • mechanical debridement alone • Er:YAG laser alone • mechanical debridement combined with antiseptic agents • mechanical debridement combined with local application of antibiotics Surgical interventions: • guided bone regeneration or use of bone substitutes Conclusions: • submucosal debridement alone may not be adequate for the removal of bacterial load from the surfaces of implants with peri-implant pockets >5 mm • the use of the Er:YAG laser can improve peri-implant clinical parameters within 6 months, but it remains unclear whether these effects can be maintained over time • the combination of minocycline and mechanical debridement appeared to provide an improved treatment outcome compared with the combination of chlorhexidine and mechanical debridement, for a short-term period of 12 months • guided bone regeneration or the application of a bone substitute (nanocrystalline hydroxyapatite) can be efficacious for the treatment of peri-implantitis lesions

of periodontitis, although other patient factors were not taken into consideration.

The limitations of the microbial findings for peri-implantitis were the heterogeneity of the studies included in the selected reviews, and the differences in sensitivity and specificity of the different microbial identification methods used. The different microbial identification methods used included culture techniques, darkfield microscopy, DNA–DNA checkerboard hybridization technique, DNA probe analysis, 16S rRNA gene sequencing technique, and polymerase chain reaction (PCR) techniques. The different detection techniques used in the studies prevent comparisons of microbial data across studies. Furthermore, most studies report the microbial data as frequency of detection and may not provide enough information to ascertain the extent of microbial involvement. In addition, there are also differences in the mode of sample

Table 6

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Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Mahato et al[36]	Inclusion: • patients with at least 1 dental osseointegrated implant affected by peri-implantitis • a clinical intervention treating peri-implantitis • a pathological condition of peri-implantitis with bone loss • human studies • randomized and controlled clinical trials • follow-up of at least 6 months Exclusion: • not in English Quality: • quality was assessed using the Critical Appraisal Skills Program and PRISMA-2009 Checklist • potential language bias as only English studies included	Characteristics of interventions: Nonsurgical interventions: • mechanical surface debridement using carbon or titanium curettes with or without surface decontamination, systemic antibiotics, some additional adjunctive therapies agents or other devices like lasers • mechanical surface debridement using carbon or titanium curettes, laser light, and antibiotics Surgical interventions • resective, regenerative, or a combination • implantoplasty, elevation of mucoperiosteal flap, and removal of peri-inflammatory granulation tissue followed by surface decontamination and bone grafting Conclusions: • non-surgical therapy tends to remove only the local irritant from the peri-implantitis surface with or without some additional adjunctive therapies and is not helpful in osseous defects • surgical therapy in combination with osseous resective or regenerative approach removes the residual sub-gingival deposits additionally reducing the peri-implantitis pocket • there is no specific recommendation for the treatment of peri-implantitis, but surgical therapy in combination with osseous resective or regenerative approach showed positive outcome
Muthukuru et al[38]	Inclusion: • at least 1 osseointegrated implant with a definitive restoration that presented with signs of peri-implantitis • peri-implantitis was defined as peri-implant crestal bone loss at osseointegrated dental implants in conjunction with inflammation of peri-implant mucosa[17]	Characteristics of interventions: Nonsurgical interventions: • mechanical submucosal debridement using hand instruments, sonic instruments, ultrasonic instruments, and air polishing • locally applied antiseptics • local delivery or systemic administration of antibiotics • lasers • host modulation therapy Conclusions: • locally delivered antibiotics (minocycline microspheres or doxycycline hyclate) as an adjunct to submucosal debridement may result in greater reduction in BOP scores and PDs compared with submucosal debridement with adjunctive submucosal irrigation with chlorhexidine digluconate. • Er:YAG laser treatment may result in greater reduction in BOP scores compared with submucosal debridement with adjunctive submucosal irrigation with chlorhexidine digluconate • submucosal glycine powder air polishing may reduce BOP scores to a greater extent than submucosal irrigation with chlorhexidine digluconate as an adjunct to submucosal debridement with hand instruments and showed no different clinical outcomes compared with Er:YAG laser treatment • the available information is insufficient to suggest whether any of the assessed non-surgical treatments arrest bone loss in implants with peri-implantitis

collection; some studies use paper points whereas other studies use curettes.

The microbiologic analysis of the peri-implantitis sites can be divided into 2 types: studies that tested for target pathogens and studies that evaluated the entire microbiome.[42] Metagenomic and metatranscriptomic techniques that analyze the entire microbiome included 16S pyrosequencing[63] and use of the 16S gene clone library[64] to test for a wide range of

TABLE 6

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Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Natto et al[39]	Inclusion: • human study between 2002 and Jan 2014 • published in English • at least 6 months of follow-up • the use of any type of dental laser (Er:YAG, CO_2, Nd:YAG, Er,CR:YSGG, or diode) • any or all control treatments • at last 1 restored osseointegrated implant with peri-implantitis Quality: • quality and strength of evidence assessed based on the criteria from the Agency for Healthcare Research and Quality[62]	Characteristics of interventions: Surgical and non-surgical interventions: • Er:YAG lasers • CO_2 lasers • Er,CR:YSGG lasers • diode lasers Conclusions: • based on limited data, the Er:YAG and CO_2 lasers • can improve the outcome of peri-implantitis treatment for up to 6 months, but the evidence is not sufficient
Ramanauskaite et al[44]	Inclusion: • nonsurgical and surgical treatment outcomes for peri-implantitis in patients with at least 1 osseointegrated rough-surface, solid screw-type implant that presented the signs of peri-implantitis • reported clear data and followed up for at least 6 months on clinical and radiographic peri-implant tissue parameter changes • all human prospective or retrospective follow-up studies and clinical trials, cohort studies, case control studies, and case series studies were included with at least 10 patients • studies from which smokers were not excluded • treatment outcomes had to include changes in PD and or BOP as primary outcome variables and or radiologic bone level changes/bone defect fill as a secondary outcome variable Exclusion: • in vitro and animal studies; studies based on charts or questionnaires • studies of patients with immunologic diseases, uncontrolled diabetes mellitus, osteoporosis, or other contraindicating systemic conditions • studies of patients with machined and hydroxyapatite surface implants or ceramic implants • studies including fewer than 10 patients • studies involving less than 6 months of follow-up after peri-implantitis treatment • studies not focused specifically on the selected topic or that included unclear data or had authors who could not be contacted for any reason Quality: • the Cochrane Collaboration's 2-part tool for assessing risk of bias[56] was used to assess bias across the studies and identify papers with intrinsic methodologic and design flaws - most of the studies were classified as unclear risk and a few studies were judged to have a high risk of bias	Characteristics of interventions: Nonsurgical interventions: • submucosal scaling with piezoelectric ultrasonic scaler, or subgingival air polishing compared with the hand instrumentation using either carbon fiber or titanium curettes • adjunctive local delivery of minocycline microspheres • laser therapy using Er:YAG laser • photodynamic therapy as an adjunct to mechanical debridement Surgical interventions: • surgical treatment methods were divided into 3 groups: access surgery, resective surgery, and regenerative surgery • for the regenerative approach: procedures involved bone grafts (xenogenous, autogenous, or allogenous), with or without barrier membranes Conclusions: • the meta-analysis demonstrated improved bleeding on probing after non-surgical treatment but did not reveal a statistically significant difference in the probing depth changes • there was a significant improvement in probing depth and bleeding on probing values after surgical treatment and an intra-bony defect fill was found to be 1.66 mm using a regenerative treatment modality • the meta-analysis confirmed a significant reduction in radiologic peri-implant marginal bone level after nonsurgical, resective, and regenerative surgical treatment • regenerative surgical treatment of peri-implantitis was found to be most effective

microorganisms. Many of the studies included in the selected systematic reviews only tested for target pathogens. Studies that only test for target pathogens will lack the data pertaining to the overall microbial composition in peri-implantitis. Thus, without more studies with a comprehensive analysis of the phylogenetic and taxonomic bacterial diversity that exist in the peri-implantitis sites, the conclusions drawn in the systematic reviews on the microbial findings will be limited.

The conclusions derived from most of the systematic review pertaining to peri-implantitis treatment also needed to be interpreted with caution. This was because the number of included studies for each surgical or non-surgical procedure was too low to enable strong statistical analysis. Furthermore, only some of the included systematic reviews comprised studies that compared treatment effects of different approaches. The included studies have various degrees of heterogeneity in study design, case selection, and treatment. Since no methodology was established as the gold standard for the

Table 6
Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Sahrmann et al[45]	Inclusion: • RCT studies comparing interventions using membrane and bone graft substitutes to control groups treated without GBR techniques • nonrandomized clinical trials, and case reports and series • Only cases treating bone defects derived from marginal peri-implantitis were considered. Studies dealing with periapical peri-implantitis were not included because of its different etiology and therapeutic approaches. Exclusion: • animal studies, review articles, missing peri-implantitis situation, or peri-implantitis treatment • treatment with only membrane or only bone graft substitute or none of both • in vitro studies	Characteristics of interventions: Surgical interventions: • during surgery, most of the studies used plastic or carbon curettes for mechanical debridement, while some studies used an ultrasonic scaler, rotating instruments, air powder, or soft laser treatment • GBR techniques used different types of membranes (diverse synthetic membrane products, resorbable bovine, or porcine collagen) in combination with different bone substitutes (DFDBA, DFDBA in combination with PepGen and platelet-rich plasma, autogenous bone, hydroxyapatite, bovine xenografts, and algae-derived calcium carbonate Conclusions: • complete fill of bony defects caused by peri-implantitis using a GBR protocol with membrane and bone graft substitutes does not seem to be a predictable outcome, although a partial defect fill can be expected • published peri-implantitis literature lacks comprehensive studies with a high number of cases that would enable a sound statistical analysis • RCT studies comparing GBR treatment to noninvasive debridement in peri-implantitis cases are needed to provide evidence for an additional benefit of the use of bone graft substitutes and membranes • complete fill of the bony defect using GBR seems not to be a predictable outcome
Schwarz et al[46]	Inclusion: • English language • prospective RCT or non-randomized CCT studies (split-mouth or parallel group designs) in humans comparing alternative or adjunctive measures to conventional nonsurgical or surgical treatments • data on the clinical changes in mucosal inflammation and probing PD following nonsurgical or surgical treatments Exclusion: • inclusion of <5 patients • inadequate case definition • lack of clinical data on the changes in mucosal inflammation and PD Quality: • quality assessment of all selected full-text articles was performed according to the Cochrane collaborations tool for assessing risk of bias • the percentages across all included studies for high, low and unclear risk of bias items were 34.1%, 54.8%, and 11.1 %, respectively	Characteristics of interventions: Nonsurgical interventions for peri-implantitis: • mechanical/ultrasonic debridement • alternative measures for biofilm removal • adjunctive antiseptic therapy • adjunctive antibiotic therapy • alternative measures for surface decontamination • adjunctive resective therapy • adjunctive augmentative therapy Surgical interventions: • open flap debridement Conclusions: • alternative/adjunctive measures may improve the efficacy of conventional treatments at peri-implantitis sites • adjunctive resective and or augmentative measures were promising but needed further investigations

treatment of peri-implantitis, the majority of studies were designed as a comparison between 2 completely different types of intervention rather than between a recognized control. This reduced the clinical implications even in the higher quality studies. Also, in a systematic review of treatment effectiveness, it is unacceptable that the definition of peri-implantitis was not standardized across studies. In addition, a high risk of bias can result in an exaggeration of treatment effect, and coupled with a low level of trials reporting, this can lead to a significant overestimation of intervention efficacy.

Conclusions

In view of the limitations of the included systematic reviews, the outcome of this overview suggested the following:

(1) There was a higher occurrence of peri-implantitis after 5 years of implant function.
(2) There was a higher occurrence of peri-implantitis in patients with aggressive periodontitis, chronic periodontitis or a history of periodontitis compared to non-periodontitis patients.

Table 6
Continued

Study	Inclusion and Exclusion Criteria/Quality Assessment	Results/Conclusion
Suárez-lópez del Amo et al[49]	Inclusion: • non-surgical treatment outcomes for peri-implant mucositis and peri-implantitis in patients with at least 1 osseointegrated solid screw-type implant (only peri-implantitis data reported for this review) • human prospective studies, clinical trials, cohort studies, case control, and case series studies • at least 10 implants • at least 6-month follow-up • clinical and or radiographic changes reported • treatment outcomes reporting changes in probing depths and or bleeding on probing and or radiographic bone level changes Exclusion: • case reports, retrospective investigations, in vitro, and animal studies • less than 10 implants • less than 6 months of follow-up • surgical treatment of peri-implantitis • human trials with missing information or unclear data Quality: • Cochrane Collaboration's tool for assessing risk of bias in randomized trials • Newcastle–Ottawa scale was used to evaluate the methodological quality of nonrandomized studies	Characteristics of interventions: Nonsurgical interventions for peri-implantitis: • oral hygiene instructions using interdental brushes or other required techniques indicated in the protocol before initiating different treatment modalities • self-performed cleaning techniques including certain toothpaste and toothbrush • systemic administration of antimicrobial agent, or locally delivered antibiotics or antimicrobial adjunct to scaling and root planning and air-polishing • laser, photodynamic therapy, supra-/sub-mucosal mechanical debridement, and air-abrasive devices in conjunction to scaling and root planning • lasers used were diode laser, Er:YAG laser, and light-activated disinfection treatment Conclusions: • modest and unpredictable outcomes are expected for non-surgical treatment for peri-implantitis lesions

*RCT, randomized controlled trials; CONSORT, Consolidated Standards of Reporting Trials; GBR, guided bone regeneration; PD, probing depth; Er:YAG, erbium-doped yttrium aluminium garnet laser; CTs, clinical trials; PPD, probing pocket depth; CAL, clinical attachment level; ROB, Risk of Bias; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; CCT, controlled clinical trials; CHX, chlorhexidine; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CO_2, carbon dioxide; Nd:YAG: neodymium-doped yttrium aluminium garnet; DFDBA, demineralized freeze-dried bone allograft.

(3) There was a higher occurrence of peri-implantitis in smokers compared to non-smokers.
(4) IL-1β release and TNF-α release was significantly higher in peri-implantitis compared to healthy peri-implant mucosa.
(5) The microbiologic profile of peri-implantitis is different from periodontitis and may include *A actinomycetemcomitans*, *P gingivalis*, *P intermedia*, *T forsythia*, *T denticola*, *T socranskii*, *S aureus*, *S anaerobius*, *S intermedius*, *S mitis*, human herpesvirus 4 and 5, Epstein–Barr 1, and human cytomegalovirus 2. The microorganisms active in peri-implantitis are not limited to only periodontopathic pathogens and may involve some opportunistic pathogens.
(6) Patients with uncontrolled diabetes and cardiovascular disease have a higher risk of peri-implantitis, but there was no association between rheumatoid arthritis and the risk of peri-implantitis.
(7) Any other single or combined non-surgical interventions were better in peri-implantitis treatment than debridement alone.
(8) Surgical treatment of peri-implantitis can reduce probing depths.
(9) Guided bone regeneration can be unpredictable in peri-implantitis treatment.
(10) Different combination of adjunctive treatments for surgical and non-surgical interventions can produce successful peri-implantitis treatment outcomes.
(11) There was no strong evidence to suggest the most effective treatment intervention for peri-implantitis.
(12) Postimplant maintenance may be necessary to reduce the occurrence of peri-implantitis in high-risk patients.
(13) More randomized controlled trials using standardized definitions for peri-implantitis were needed for all forms of peri-implantitis treatment interventions.

Abbreviations

AMSTAR: A MeaSurement Tool to Assess systematic Reviews
BOP: bleeding on probing
CCT: nonrandomized controlled trials
CONSORT: Consolidated Standards of Reporting Trials
DFDBA: demineralized freeze-dried bone allograft
Er,CR:YSGG: erbium, chromium: yttrium–scandium–gallium–garnet
Er:YAG: erbium: yttrium–aluminum–garnet
FES: fully edentulous subjects
GBR: guided bone regeneration
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
IL: interleukin
IL-1β: interleukin-1 beta
NRP: non-residual pocket
PCR: polymerase chain reaction

PD: probing depth
PES: partially edentulous subjects
PICF: peri-implant crevicular fluid
PPD: probing pocket depth
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trials
RP: residual pocket
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
TNF-α: tumor necrosis factor alpha

Note

MT, JC, BEB, and JBS declare that they have no competing interests with regard to the content of the manuscript.

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